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Heritability of Attention Problems in Children: I. Cross-Sectional Results From a Study of Twins, Age 3–12 Years

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Multiple twin studies of attention problems (AP) from the Child Behavior Checklist or ADHD from the DSM criteria have reported on the genetic and environmental influences on these behaviors. The majority of these have studied AP and ADHD symptoms in twin samples combined across wide age spans, combined rater information and both genders. Thus, it is possible that the results are complicated by developmental, informant, and gender differences. The purpose of this study was to assess for the genetic and environmental contributions to overactive behavior (a syndrome highly related to AP in 7-, 10-, and 12-years olds) in 3-years olds (3,671 twin pairs), and attention problems in 7- (3,373 twin pairs), 10- (2,485 twin pairs), and 12-years olds (1,305 twin pairs) while controlling for developmental, gender and rater contrast contributions. Using a cross-sectional twin design, contributions from genetic additive, genetic dominance, unique environmental and rater contrast effects were estimated for CBCL maternal reports. We found that genetic influences on overactive behavior and attention problems are high across an age span that covers preschool and elementary school age. Although girls display less problem behavior compared to boys, heritability estimates were found equal for both genders at each age. Environmental experiences that are unique to the individual accounted for the remaining influence. At the age of 3 years, a rater contrast effect was detected. We hypothesize that the contrast effect represents a maternal rater bias effect that is dependent on the age of the twins. The implications of these findings are discussed with reference to the clinical setting and in the context of future research.

KEY WORDS: ADHD; genetics; rater bias; pre-school; schoolage

INTRODUCTION

In order to identify genes that contribute to the etiology of a common disorder such as Attention Deficit Hyperactivity Disorder (ADHD), molecular geneticists must study the relations between the genes of risk in individuals who suffer from the disorder versus individuals who do not. Thus the success of the gene finding expedition depends on the ability to identify those who do and do not have the condition of interest. Although molecular genetic techniques have advanced to the point that identifying genes of risk for child psychiatric disorders is a fairly simple laboratory exercise, our ability to provide accurate diagnoses remains a challenge [Hudziak, 2002]. With recent conflicting reports of molecular genetic contributions to ADHD [Barr et al., 2001] and the almost certain fact that common child psychiatric conditions like ADHD are due to multiple genes and environmental stimuli [Faraone and Doyle, 2001], the need for a clear phenotype (diagnosis) is evident. Obstacles to identifying genetic contributions to child psychopathology include developmental confounds, gender confounds, and rater bias confounds. Each is addressed in some detail.

Developmental confounds exist if the taxonomy does not take into account that behavior changes across development. Clearly, we must understand normal development to design developmentally sensitive phenotypic measures of child psychopathology. For example,

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it may not be appropriate to apply some of the criteria for ADHD to 3-years olds (e.g., "often fails to give close attention to details" or "makes careless mistakes in schoolwork"). Similarly, the hyperactivity items of ADHD are widely acknowledged to be less prevalent in older subjects [Biederman, 1998]. Unless we have a strategy that can establish levels of behavior in the normal population and then relate the behavior of 3-years olds to that of 7-, 10-, and 12-years olds, true cases may be misidentified. Failure to control for these differences could lead to incorrect measurements of changing phenotypes. Such measurement errors may produce excessive false positives or false negatives depending on a subject's developmental level. In this study, we analyze data on same aged twins studied together at successive developmental periods. For each age, the Child Behavior CheckList [CBCL; Achenbach, 1991] was used as assessment instrument.

Gender confounds exist when the study fails to consider that the condition may manifest differently in females than in males. Genetic studies of childhood psychopathology should allow for potential gender differences in the manifestation of genotypes. According to Hartung and Widiger [1998], of the 21 disorders usually first diagnosed in infancy, childhood, or adolescence for which sex ratios are provided, 17 have higher prevalence in boys than girls. They enumerated several sources of error which could generate or exaggerate gender differences in rates of psychopathology, most notably sampling biases and biases within the diagnostic criteria, concluding that "there may not be a mental disorder for which there are not important gender differences in the manner in which the disorder is expressed." This seems especially true for the study of ADHD, which is three to six times more prevalent in boys than girls [Offord et al., 1987]. Gaub and Carlson [1997] affirmed that research on gender differences in ADHD is badly needed, with emphasis on the potential confounding effects of referral bias, comorbidity, development, diagnostic procedures, and data source. In this study, we test for gender–genetic and gender–environment interactions in order to determine if there are gender differences in influences on overactivity (3-years olds) and attention problems (7-, 10-, and 12-years olds).

A third confound is rater bias: Does the taxonomic approach bias the selection of true cases? Prior twin studies on ADHD have reported that the best fitting biometric models are ones that include additive genetic (A), unique environmental (E), and rater contrast effects (b). Eaves et al. [1997], and Thapar et al. [2000] have reported large rater contrast effects on ADHD and related symptoms. The presence and magnitude of rater contrast effects can play a major role in the selection of true cases of ADHD [Hudziak, 2001]. Large rater contrast effects result in the underidentification of true cases, and undermine gene-finding efforts [Eaves et al., 2000]. In this study, we test for rater contrast effects by gender and age in large samples of Dutch twins who were recruited to participate in developmental genetic studies shortly after birth.

CURRENT RESEARCH

The purpose of this study is to extend our prior work on genetic influences on behavior problems from the CBCL by analyzing data from an epidemiological twin study, using ratings from mothers obtained when the twins were 3, 7, 10, and 12 years of age. Because of the large sample size, we can test for age, gender, and contrast effects on the genetic and environmental influences on overactivity and attention problems. With this work, we ask the following questions: What are the genetic and environmental contributions to overactivity and attention problems at ages 3, 7, 10, and 12? Are the genetic contributions similar in magnitude? Are there differences in the genetic and environmental influences by gender? Do contrast effects vary across this 9 years developmental period, that is, do mothers have different response habits when rating their 3-year-old versus their 12-year-old children?

MATERIALS AND METHODS

Subjects and Procedure

The study is part of an ongoing twin-family study of the development of behavioral and emotional problems in the Netherlands. The subjects are all part of The Netherlands Twin Registry [NTR; Boomsma, 1998]. For this study, we have assessed a sample of Dutch twin pairs whose parents (or primary caregiver) reported on their behavior when the twins were 3, 7, 10, and 12 years old. Birth cohorts 1986–1991 participated in the collection of 3- and 7-year questionnaires. For the 10-years olds, questionnaire collection was completed for birth cohorts all through 1990 and for 12-year-old twins, questionnaires were available from cohorts 1986 to the first months of 1989. The assessment procedures for the ages 7, 10, and 12 were identical to those at the age of 3 years. Parents were sent a questionnaire and were asked to return it to the NTR by mail. Parents who did not return the forms within 2 months received a reminder and persistent non-responders were contacted by phone 4 months after the initial mailing. This procedure resulted in 80% continued participation from age 3–7, 7–10, and 10–12 years. A small number of families participated at one age only (age 3, 14%; age 7, 12%; age 10, 4%; and age 12, 3%). Families that skipped at least one assessment wave make up the remaining percentages. Around 2% of the total sample of 9,160 individuals suffered from a disease or handicap that interfered severely with daily functioning. These twins and their co-twins were excluded from the genetic analyses. This left a sample of 3,853, 3-year-old pairs; the sample size for 7-year questionnaire data is 3,427 pairs, for the 10-year-old data is 2,504 pairs, and for 12-year-old data is 1,307 pairs. Zygosity was determined by DNA analyses or blood group polymorphisms for 713 same-sex twin pairs. For the remaining same-sex twin pairs, zygosity was determined by discriminant analysis of questionnaire items [Rietveld et al., 2000]. Missing values were assigned to those twin pairs with incomplete information. A small number of pairs were left unclassified because their zygosity status at one age did

not agree with their zygosity status at another age. The total number of pairs, by gender, zygosity, and age are presented in Table I. Twins with unknown zygosity were left out of the genetic analyses.

Measure

The CBCL is a standardized questionnaire for parents to report the frequency and intensity of behavioral and emotional problems exhibited by their child in the past 6 months. The questionnaire that is used for the 3-year-old twins consists of 100 problem items (CBCL/2-3) and the questionnaires that are used for the 7-, 10-, and 12-year-old twins consist of 120 problem items for parents to score (CBCL/4-18). Parents rate each behavior on a 3-point scale: 0 indicates responses of "not true," 1 "somewhat or sometimes true," and 2 "very true or often true." Dutch syndrome scales for the CBCL/2-3 were derived by both exploratory and confirmatory factor analyses using three groups of children; a clinical sample, a community sample and a sample of twins that participate in the present study [Koot et al., 1997]. This series of analyses resulted in the formation of a Dutch overactive scale, for which there is no American equivalent. The overactive scale is composed of 5 items. These items are "can't concentrate," "can't sit still," "constantly seeks help," "quickly shifts activity," and "refuses active games." Twins with more than one item missing were assigned missing value to their overall overactive scale. Around 4% of the mothers provided incomplete information on the overactive items. For the CBCL/4-18, the attention problem scale (AP) was composed according to the 1991 profile [Achenbach, 1991]. Though the majority of the 11 items of the AP scale relate to inattention, some also assess impulsivity and hyperactive behavior. In the present study, subjects with more than three missing items were not included in the analyses. This occurred in less than 2.5% of the returned questionnaires filled out by the mother when the twins were aged 7, 10, and 12 years. To facilitate reading overactive behavior at the age of 3 years is referred to with the abbreviation OA and attention problems at the older ages is referred to with AP. An association between a high score on the AP scale (a T-score of 67 is often applied as the borderline cut-off) and ADHD as assessed by the DSM is reported by numerous studies [Bird et al., 1988; Edelbrock and Costello, 1988; Steingard et al., 1992; Biederman et al., 1993; Chen et al., 1994; Hudziak et al., 2002, in review].

TABLE I. Number of Twin Pairs, by Age, Gender, and Zygosity

	Age (years)			
Zygosity	3	7	10	12
MZM	621	590	452	246
DZM	583	530	392	201
MZF	708	676	526	287
DZF	536	528	380	200
DOS	1,223	1,049	735	371
Unknown	182	54	19	2
Total	3,853	3,427	2,504	1,307

Statistical Analyses

The OA score and AP score was obtained by summing the item scores. Means, standard deviations, and twin correlations among scores were calculated using SPSS/Windows 10.0. Differences in mean scores between genders, between zygosities and across age were assessed by likelihood-ratio chi-square (χ^2) tests using the statistical software program Mx [Neale, 1997]. These tests are performed by taking into account the dependency that exists between scores from twins. PRELIS 2 [Jöreskog and Sörbom, 1993] was employed to compute the variance-covariance matrices of the observations, separately for each sex-by-zygosity group. These matrices were used as input for genetic modeling. Using the program Mx, structural equation modeling was employed to obtain an estimate of the genetic and environmental contributions to the observed variances and covariances between measures. Parameter estimates are produced such that the likelihood of the covariance structure under a given structural model is maximized. A normal distribution of the observed variables is assumed using this method. However, the distribution of OA and AP showed large deviation from normality. To approximate normality, the data were transformed by a square-root transformation. In this way, the method of maximum likelihood was eligible. Technical details of genetic model-fitting analyses are reviewed elsewhere [Neale and Cardon, 1992]. Analyses of the data took place by a cross-sectional design, that is, we analyzed each age-specific dataset separately.

Model Fitting

Observed variation for a particular measured characteristic or behavior can be decomposed into its latent, unobserved genetic and environmental components. The decomposition of variance takes place by comparing the degree of similarities between pairs of individuals who differ in their degree of genetic relatedness. The availability of twin data enables us to obtain estimates of the relative contribution of genes and environment to the observed variation of OA and AP measured at multiple ages. Figure 1 summarizes the fundamental univariate genetic model that underlies these analyses. This model was used to estimate the additive genetic (A, additive effects of genes at multiple loci), dominance genetic (D, interaction of genetic effects at the same loci), and non-shared environment (E, unique to the individual) effects. It was empirically tested that the environment that make members of the same household more alike was absent for each scale at each age. Therefore, we do not refer to this environmental source of variance in this report. The circles represent the latent, unmeasured factors. Correlations of 1.0 for MZ versus 0.5 and 0.25 for DZ genetic influences reflect the zygosity of the pair. Monozygotic twins share all their genetic material, and dizygotic twins share half of their additive genetic values and a quarter of their dominant genetic values. The unique or non-shared environment is by definition, uncorrelated between two members of a pair, either monozygotic or dizygotic. Estimates of the unique

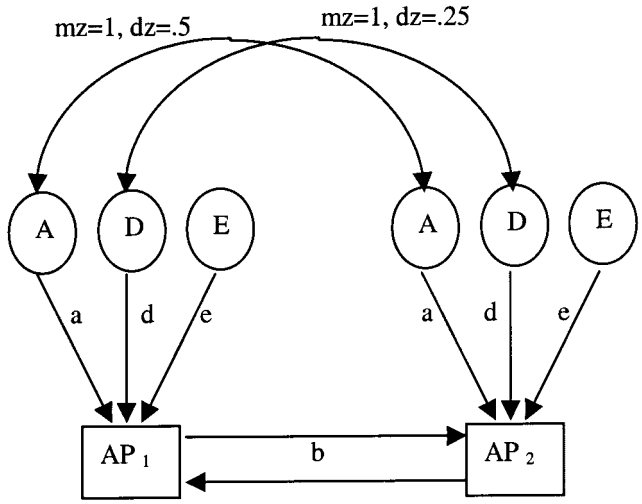

Fig. 1. Univariate path model. Note: A, additive genetic; D, dominance genetic; E, unique environment; AP_1, attention problem score of twin 1; AP_2, attention problem score of twin 2; b, contrast path.

environmental effects also include measurement error [Plomin et al., 2001].

The influence of A, D, and E on the observed variation for AP (or OA, represented in a square) is given by parameters a, d, and e. These can be considered as regression coefficients or factor loadings of AP on the latent factors A, D, and E. Squaring the factor loadings results in the absolute variance explained by each component. The sum of these squared factor loadings makes up the total variance for the observed phenotype as long as there is no evidence of interaction between genes and environment. The absolute variance explained is usually reported in a standardized form, by dividing the absolute variance by the total phenotypic variance. We then obtain a relative estimate which provide a basis for comparison with previous studies [Edelbrock et al., 1995; Schmitz et al., 1995; Rhee et al., 1999; Kuntsi et al., 2000; Thapar et al., 2000; Nadder et al., 2001].

In this univariate model, we have added a path b between the AP scores of the twins. This path implies an interaction between phenotypes. This interaction may be interpreted in two ways [Simonoff et al., 1998]. First, it may be considered a social interaction between siblings [Eaves, 1976; Carey, 1986]. That is, the behavior of one twin has a certain effect on the behavior of his or her co-twin. This effect can be either cooperative or competitive. In the former case, attention problem behavior in one twin leads to likewise behavior in his or her co-twin. In the latter case, increased attention problem behaviors in one twin lead to decreased behaviors in his or her co-twin. Second, the path may also be considered an effect introduced by the rater [Neale and Stevenson, 1989]. When parents are asked to evaluate and report upon the problem behavior of their children, they may very well compare the twins' behaviors against one another, despite instructions on the questionnaire forms. In this way, one twin becomes some kind of standard by which the behavior of the co-twin is rated. Parents may either stress the similarities or differences between the children. In like manner as the hypothesized sibling interaction, the resulting effect is either positive or negative. Based on previous research we expect this path to be negative [Thapar et al., 1995; Nadder et al., 1998; Eaves et al., 2000; Hudziak et al., 2000; Kuntsi and Stevenson, 2000; Martin et al., 2002; Price et al., submitted]. Throughout the remainder of this article, we refer to this parameter as a 'contrast effect,' to capture both mechanisms with an accurate label. Very low DZ correlations compared to MZ correlations give a first indication that a contrast effect is present. Such a pattern in correlations may also indicate the presence of non-additive genetic influences. We are able to distinguish between a contrast effect (AE-b model) and genetic dominance (ADE model) by inspection of the observed variances for MZ and DZ twins. A contrast effect leads to smaller variances for MZ compared to DZ. In case of dominance, MZ and DZ variances are expected to be of equal magnitude.

Model Fitting Procedures

Figure 1 shows the basic model for the analyses. Analyses were initiated with the fit of an ADE-b model. Next, ADE and AE-b models were applied to the data. Knowing that attention problems are not equally distributed in the population, we hypothesized upon a gender difference for the b-path. We asked ourselves if a contrast effect found for boys is equal to such an effect for girls and to opposite-sex twins. The contrast effect of the DOS twins was evaluated first. The contrast parameter was allowed to differ from those estimated for male twin pairs and female twin pairs. We next constrained the DOS contrast parameter to the mean of the contrast effect in male pairs and female pairs. For each age, we found the difference to be non-significant. Because of this uniform result, we do not report the fit of this model in our tables but have adopted this model as a baseline model, like the ADE and ADE-b model. At this stage of model fitting, all parameters were allowed to differ between genders. So, with the ADE, and AE-b models six parameters were estimated, three for each gender. The more general model, ADE-b has eight parameters specified. The ADE and AE-b are both nested within the ADE-b model. The alternative models are evaluated on the basis of their plausibility and goodness-of-fit. The goodness-of-fit index is χ^2, which indicates the statistical significance concerning the fit between expectations (model) and observations (data).

We next proceeded with the fit of reduced models, in which parameters were constrained across gender. That is, we hypothesized that the genetic and environmental effects were of equal magnitude in boys and girls. Likewise, we constrained the contrast effect in boys to equal the effect in girls. These reduced models were all nested within the models in which estimates were allowed to differ by gender. The model that describes the data best is found by comparing the goodness-of-fit of the alternative models. The degrees of freedom for this test equal the difference in the number of parameters between two nested models. If the χ^2 test is not

significant, we considered the restricted model tenable [Loehlin, 1992].

We report here the analyses based on the data from questionnaires that are completed by the mother of the twins because this is the largest dataset, and thus has greater statistical power. Due to funding limitations during some years of the study, CBCL forms were only sent to the mother of the twins. However, the paternal CBCL data were analyzed, and results that are very similar to those based on maternal reports were obtained.

RESULTS

Descriptive Statistics

Means and standard deviations for OA and AP are presented in Table II.

At all ages, mothers report more behavior problems in boys compared to girls. The difference in means was found to be significant at all ages (age 3: $\chi^2_1 = 58.15$, $P = 0.00$; age 7: $\chi^2_1 = 151.29$, $P = 0.00$; age 10: $\chi^2_1 = 119.63$, $P = .00$; age 12: $\chi^2_1 = 60.62$, $P = 0.00$). Next, we were interested whether the observed changes in mean scores across age were significant. To this end, we constrained the mean score at one age to the mean score at the following age. These three tests (age 3–7, 7–10, 10–12 years) were performed separately for each gender. It should be noted that the 3-year-old CBCL OA scale is different than the AP scale for 7, 10, and 12 year olds. For boys, we noted a significant increase in behavior problems from age 3 to 7 years ($\chi^2_1 = 60.81$, $P = 0.00$). As suggested by the very small increase in mean scores of girls, this increase did not reach significance. Likewise, from age 7 to 10 years, both boys and girls displayed stability in their degree of AP. From age 10 and beyond, we observed a decrease in reported attention problems for both genders. This change was found significant (boys: $\chi^2_1 = 25.56$, $P = 0.00$; girls: $\chi^2_1 = 29.79$, $P = .00$)

To estimate the number of children likely to meet an ADHD diagnosis, we first calculated the OA and AP distributions. Next, the raw score that corresponds to a T-score of 67 in a Dutch Community sample [Koot et al., 1997] was imposed on the distribution of the twins. The application of the community cut-off and the resulting percentages allow a comparison with the prevalence of borderline and clinical cases reported for the Dutch and other populations. Since boys differ significantly from girls on the prevalence of problems, the distributions were calculated separately by gender. In the case of the 3-year-old boys and girls, roughly 3% of the boys and 2% of the girls exceed the borderline cut-off of a T-score of greater than 67. While it may be difficult to distinguish true problematic overactive behavior of 3-years olds from age-related manifestations of normal development, the evidence suggests that between 2–3% of the children are rated as deviant on the Dutch OA scale. In comparison with other reports on pre-school rates of overactive behavior and related behavior problems, these percentages appear as quite modest [Campbell, 1995; Koot et al., 1997]. The data for the 7-, 10-, and 12-year-old age groups are more instructive. Inattention, hyperactivity, and impulsivity are more commonly diagnosed in children of these ages [Ross and Ross, 1982]. By imposing the standards of Chen et al. [1994] and using the more rigorous T-score of 67 as cut-off, around 6.5% of the boys would meet DSM criteria for ADHD at age 7 and 10 years. For girls, these numbers are 3.1% and 4.9%, respectively. At the age of 12 years, the number of children for whom DSM criteria would apply has decreased with around 1.3%.

The distributions of OA and AP display a large deviation from normal skewness and kurtosis. After square-root transformation, skewness ranged from −0.39 to 0.17 and kurtosis ranged from −0.82 to −0.59. The means based on raw scores and the variances obtained after transformation of the raw scores are summarized in Table III.

Visual inspection of Table III reveals a somewhat larger variance for dizygotic twins compared to monozygotic twins at the age of 3 years. This is observed for both boys and girls. This pattern is in line with a hypothesis of the presence of a contrast effect. The difference in variances is not observed at subsequent ages. We also note that the variance displayed by boys increases with the increasing age. For girls, the degree of variation appears to stabilize from age 7 and beyond. Means were tested in the following way; means of male DOS twins were compared to the means of DZM twins and next, dizygotic males were compared to the

TABLE II. Means and Standard Deviation (SD) Calculated Separately for Each Gender

	Boys			Girls		
	N	Mean	SD	N	Mean	SD
Age (year)						
3	3,709	2.89	2.24	3,758	2.46*	2.16
7	3,385	3.27	2.93	3,522	2.48*	2.54
10	2,456	3.23	3.09	2,593	2.38*	2.56
12	1,277	2.81	2.92	1,362	1.99*	2.29

N, number of individuals twins.
*Mean score of girls differs significantly from mean score of boys at $P < 0.05$. Reported means are not transformed.

TABLE III. Means and Variances by Zygosity and Gender

					DOS	
Age	MZM	DZM	MZF	DZF	Boy	Girl
3 year						
Mean	3.07	2.73	2.55	2.58	2.83	2.23
Variance	0.64	0.71	0.68	0.74	0.71	0.76
7 year						
Mean	3.25	3.14	2.51	2.65	3.36	2.16
Variance	0.82	0.80	0.81	0.82	0.86	0.85
10 year						
Mean	3.25	3.16	2.24	2.51	3.27	2.10
Variance	0.93	0.89	0.81	0.88	0.97	0.84
12 year						
Mean	2.84	2.72	2.11	1.97	2.86	1.17
Variance	1.02	0.90	0.74	0.78	0.93	0.82

Variances are calculated on square-root transformed means. Reported means in this table are not transformed.

monozygotic males. The same sequence of testing was applied to mean scores of female twins. The dizygotic male scores were found significantly smaller compared to monozygotic male scores at the age of 3 years ($\chi^2_1 = 8.76, P = 0.003$). More interesting is the significant difference between female DOS twins and DZF twins (age 3: $\chi^2_1 = 13.05$, $P = 0.00$; age 7: $\chi^2_1 = 20.43$, $P = 0.00$; age 10: $\chi^2_1 = 8.69$, $P = .00$). With the exception of the age of 12 years, girls with a male co-twin suffer from less OA and AP compared to girls with a female co-twin. The absence of a significant effect at the age of 12 years may have resulted from a reduced lack of power due to a smaller number of participating twins. The evaluation of means was followed by inspection of the gender-by-zygosity correlations. Twin correlations provide the initial insight into the genetic and environmental contributions to variance in OA and AP. Calculated separately for each zygosity group, correlations are reported in Table IV.

The monozygotic twins, both males and females, show large correlations of around 0.70. Quite notable is the stability observed for the monozygotic correlations. Over time monozygotic twins remain rather constant in their resemblance with respect to OA and AP. An estimation of the influence of the environment unique to the individual is obtained after subtracting the monozygotic correlation from unity. This calculation suggests that around one third of the total variance for OA and AP is explained by the unique environment. The dizygotic correlations are small, especially at the age of 3 years. Since the dizygotic correlations are less than half the monozygotic correlations, genetic dominance appears to be important. We note a steady increase in the dizygotic correlations across age. This suggests that the relative dominance genetic effect may decrease in importance when children become older. The somewhat larger dizygotic correlations for girls suggest that genetic dominance may play a larger role in explaining variance in boys as compared to girls. The correlations for the opposite sex twins are in line with the DZM and DZF correlations.

Genetic Modeling

We next turned to formal testing to evaluate the role of additive and dominance genetic effects, gender differences, and the presence of a contrast effect. The specified models and their fit indices are reported upon in Table V.

We fitted two series of models, with and without differences across gender. Because of the small DZ correlations, we argued that the resemblance between twins was more likely due to genetic additive and dominance effects instead of shared environmental effects at each age. This hypothesis was found true for each individual dataset. The model fitting results of models including a shared environmental factor are not reported here. For each individual dataset, we report upon four models that allowed parameter estimates to differ between boys and girls. These models were ADE-b, ADE and AE-b and AE. The good fit of the models that incorporated a contrast effect at the age of 3 years was in line with the earlier noted difference in variance between MZ and DZ twins at this age (see Table III). The contrast effect was found to account for a significant proportion of the total variance, evaluated by the AE model. Given our large sample size and the significant contribution of the contrast effect, there is little doubt upon the presence of the contrast effect at age 3 [Rietveld et al., in press]. However, we lack sufficient power to establish whether D, in addition to the contrast effect, is a necessary source of variance. A model with dominance alone was found insufficient to describe the data.

TABLE IV. Correlations by Age, Gender, and Zygosity

	Age (year)			
	3	7	10	12
MZM	0.63*	0.68*	0.70*	0.75*
DZM	0.08	0.15*	0.20*	0.25*
MZF	0.63*	0.70*	0.70*	0.70*
DZF	0.07	0.23*	0.30*	0.31*
DOS	0.11*	0.26*	0.28*	0.25*

*Correlation is significant at the 0.01 level.

At ages 7, 10, and 12 years, the AE-b model described the data as well as the ADE and ADE-b models. Based on the χ^2, degrees of freedom, and P-value, no distinction between these models could be made. The importance of the contrast parameter and the genetic dominance parameter was formally tested by the application of the AE model. The significant increase in χ^2 indicated the necessary inclusion of the contrast effect or genetic dominance effect or both the effects at the age of 7 and 10 years. This outcome was opposed to the outcome found for the oldest age group; the AE model did not lead to a significant deterioration in fit. However, because the age 12 years comprises the smallest sample size, we may have insufficient power to detect the presence of D. Therefore, we maintain both the ADE and AE model as best fitting models. Parameter b was estimated at 0.01 in the ADE-b model and we consider this effect as non-existent.

Parameters were constrained across gender in the next series of analyses. These reduced models were all nested with the full models, so the difference in χ^2 and degrees of freedom were used to identify the best fitting model. The examination of gender differences resulted in outcomes that varied with the age. Concluding, for the youngest age groups, no gender differences were found. The best fitting model at the age of 3 years was one that included the contrast parameter, AE-b and ADE-b. At the age of 7 years, we could not distinguish between an ADE-b, AE-b and an ADE model. For the oldest two age groups, the magnitude of the genetic and environmental effects was found to depend on gender. At the age of 10 years, in line with the age 7 years, ADE-b, AE-b, and ADE models were considered best fitting. The ADE-b model and the AE-b model was further reduced by specifying the contrast effect in boys to equal the effect in girls ($\Delta\chi^2 = 0.40$, df $= 1, P > 0.05$; $\Delta\chi^2 = 1.02$, df $= 1$, $P > 0.05$, respectively). Since the models differ much in their interpretation and because we lack sufficient power to distinguish between the models we report and discuss all three models. At the age of 12 years,

TABLE V. Model Fitting Results

		χ^2	df	P	Comparison	Change in χ^2 (df)
Age 3 year	With sex. diff.[a]					
1.	ADE-b	1.75	7	0.97		
2.	ADE	12.84	9	0.17	1.	11.09 (2), $P < 0.05$
3.	AE-b	1.93	9	0.99	1.	0.18 (2), ns
4.	AE	101.24	11	0.00	2.	88.4 (2), $P < 0.05$
					3.	99.31 (2), $P < 0.05$
	No sex. diff.[b]					
4.	**ADE-b**	**4.98**	**11**	**0.93**	**1.**	**3.23 (4), ns**
5.	ADE	16.29	12	0.00	5.	11.31 (1), $P < 0.05$
6.	**AE-b**	**5.14**	**12**	**0.95**	**5.**	**0.16 (1), ns**
Age 7 year	With sex. diff.[a]					
1.	ADE-b	7.54	7	0.38		
2.	ADE	7.96	9	0.54	1.	0.42 (2), ns
3.	AE-b	8.71	9	0.44	1.	1.17 (2), $P < 0.05$
4.	AE	32.14	11	0.00	2.	24.18 (2), $P < 0.05$
					3.	23.43 (2), $P < 0.05$
	No sex. diff.[b]					
5.	**ADE-b**	**10.14**	**11**	**0.52**	**1.**	**2.60 (4), ns**
6.	**ADE**	**10.30**	**12**	**0.59**	**5.**	**0.16 (1), ns**
7.	**AE-b**	**10.93**	**12**	**0.54**	**5.**	**0.79 (1), ns**
Age 10 year	With sex. diff.[a]					
1.	**ADE-b**	**6.13**	**7**	**0.53**		
2.	**ADE**	**6.70**	**9**	**0.67**	**1.**	**0.57 (2), ns**
3.	**AE-b**	**6.44**	**9**	**0.70**	**1.**	**0.31 (2), ns**
4.	AE	18.86	11	0.06	2.	12.16 (2), $P < 0.05$
					3.	12.42 (2), $P < 0.05$
	No sex. diff.[b]					
5.	ADE-b	17.19	11	0.10	1.	11.06 (4), $P < 0.05$
Age 12 year	With sex. diff.[a]					
1.	ADE-b	5.28	7	0.63		
2.	**ADE**	**5.57**	**9**	**0.78**	**1.**	**0.29 (2), ns**
3.	AE-b	7.57	9	0.58	1.	2.29 (2), ns
4.	**AE**	**10.17**	**11**	**0.52**	**2.**	**4.60 (2), ns**
					3.	**2.60 (2), ns**
	No sex. diff.					
5.	ADE	25.49	12	0.01	2.	19.92 (3), $P < 0.05$
6.	AE	29.16	13	0.01	4.	18.99 (2), $P < 0.05$

Best fitting models are in bold.
[a]Contrast parameter DOS is constrained to equal mean of male twin pairs and female twin pairs.
[b]Contrast parameter males is equal to females.

gender differences were detected for the ADE and AE model.

In addition to the genetic modeling of transformed data, we also adopted an alternative approach. Given the nature of the questionnaire items, one may argue that the CBCL measures only half of the distribution of OA and AP. That is, the questionnaire items relate to problem behavior only and do not measure the presence of "good concentration skills" or "excellent school work." From this point of view, we considered OA and AP to have an underlying continuity with a normal distribution. This underlying variable has been called the liability [Falconer and Mackay, 1996]. We created multiple categories with thresholds separating them. If a twin's score exceeds a certain threshold, he or she manifests the signs and symptoms that fit in with the next OA or AP category. It is assumed that many causes of variation, both genetic and environmental in origin combine to give the liability. Given that the manifestation of OA and AP is due to multiple causal factors [Faraone and Doyle, 2001], the liability model appears an adequate approach to analyze the data. This alternative approach, the application of the liability model, resulted in identical relative estimates for the genetic and environmental contributions to variance.

The contrast effect, and absolute estimates of the additive genetic, dominance genetic, and unique environmental contributions to the total variance are summarized in Table VI.

Varying with age and specified model, the contrast effect is estimated between -0.14 and -0.02. We find the largest effect at the age of 3 years, which decreases rapidly to insignificant at the age of 12 years. An accompanying interesting outcome is that the contrast effect was found to be of equal importance in boys and girls. This implies that, whether the contrast effect is considered a true interaction between siblings or a bias introduced by the parents, the twins' gender is of no importance. We report upon the absolute estimates of genetic and environmental variance for two reasons. First, these estimates clearly illustrate the significant gender differences that were detected at the age of 10 and 12 years. The total variance, calculated by summing the additive, dominance genetic and unique environmental effects, is much larger for boys as compared to girls. The gender difference appears strongest

TABLE VI. Estimates of Absolute Variance Components and Contrast Parameter

		Additive genetic	Unique environment	Dominance genetic	Total variance	Contrast
Age 3 year						
Boys/girls	ADE-b	0.464	0.200	0.097	0.761	−0.12
	AE-b	0.582	0.190	—	0.772	−0.14
Age 7 year						
Boys/girls	ADE-b	0.373	0.231	0.233	0.837	−0.02
	ADE	0.263	0.242	0.320	0.825	
	AE-b	0.658	0.212	—	0.870	−0.06
Age 10 year						
Boys	ADE-b	0.421	0.263	0.255	0.939	−0.02
Girls	ADE-b	0.526	0.224	0.093	0.843	
Boys	ADE	0.296	0.274	0.356	0.926	
Girls	ADE	0.424	0.234	0.172	0.830	
Boys	AE-b	0.721	0.274	—	0.968	−0.05
Girls	AE-b	0.661	0.208	—	0.869	
Age 12 year						
Boys	ADE	0.344	0.296	0.316	0.956	
Girls	ADE	0.528	0.217	0.035	0.780	
Boys	AE	0.653	0.313	—	0.966	
Girls	AE	0.564	0.221	—	0.785	

A, additive genetic; D, dominance genetic; E, unique environment; −b, contrast parameter.

for the genetic dominance effect. Girls have much smaller estimates as compared to boys. Based on the twin correlations, we had speculated on such a reduced importance of the dominance effect with increasing age for the girls. For the AE and AE-b models, the ratio additive genetic effects to unique environmental effects appears equal across gender. Such an equal ratio will result in similar relative estimates for the boys and girls. A second reason for the report of absolute estimates of variance has to do with the contrast effect. The absolute estimates presented here are applicable to twins, and given that these twins are representative of the population in general, to singletons. The absolute estimates are used for the calculation of the relative influences of genes and environment. With relative we mean the effect of a certain source of variance expressed as a proportion of the total variance. In our "Method" section, we mentioned that the contrast effect causes the total variance of a phenotype to depend on the genetic relationship of the individuals that are being rated. Because the effect is negative, monozygotic twins have smaller variances compared to dizygotic twins. The variance induced by the contrast effect is controlled for when we report upon the genetic and environmental influences for singletons. So, for models including a contrast effect, the calculation of relative estimates results in estimates that differ between MZ twins, DZ twins, and singletons. These relative estimates are shown in Table VII, separately for three groups of individuals who vary in genetic relatedness with one another.

Relative estimates are reported for MZ twins, DZ twins, and singletons for any model including the contrast effect. Because total variances are equal across pairs of varying genetic relatedness in the absence of a contrast effect, estimates derived from the fit of ADE and AE models are reported for singletons only. When the contrast effect is small (age 7 and 10 years), we barely note the differences in relative estimates across twins and singletons. When the contrast effect is large (age 3 years), the proportions of the total variance that is explained by genetic and environmental effects differ between MZ twins, DZ twins and singletons.

Consistent across age, gender, and model, genetic effects are most important in explaining observed variance in OA and AP. Broad heritability, the sum of additive and dominance genetic effects, varies between 68% and 76% of the total variance. From a power study, we have learned that when D is excluded from the model, the heritability and contrast effect estimated by the AE-b model may have been biased upwards [Rietveld et al., in press]. Likewise, ignoring the presence of a contrast effect by accepting an ADE model may have lead to inflated estimates of heritability [Eaves et al., 1997]. The residual variance is explained by the unique environment, whereas the importance of the additive and dominance effect varies with the age, the unique environmental effect continues to account for around one third of the variance across the age. The stability of the magnitude of the unique environmental effects was already suggested by the stable difference between unity and the MZ correlations.

DISCUSSION

In this study, the genetic and environmental contributions to attention problem behavior are estimated by taking advantage of large sample sizes of twin pairs for separate age cohorts. We asked and answered the following questions: What are the genetic and environmental contributions to overactivity at the age of 3 years and attention problems at ages 7, 10, and 12 years? Are these contributions of equal magnitude at each age, or do they vary as a function of age? Are there differences in the genetic and environmental influences by gender? Finally, models were fitted that allowed to test for contrast effects, in order to determine if maternal rating habits or interaction among siblings takes place. Each issue is presented in some detail. The report is completed

TABLE VII. Estimates of Relative Variance Components

		Additive genetic			Unique environment			Dominance genetic		
		MZ (%)	DZ (%)	Singletons (%)[a]	MZ (%)	DZ (%)	Singletons (%)[a]	MZ (%)	DZ (%)	Singletons (%)[a]
Age 3 year	ADE-b	57	59	61	31	28	26	12	13	13
Boys/girls	AE-b	69	73	75	31	27	25	—	—	—
Age 7 year										
Boys/girls	ADE-b	44	44	44	29	28	28	27	28	28
	ADE	—	—	32	—	—	29	—	—	39
	AE-b	73	74	76	27	26	24	—	—	—
Age 10 year										
Boys	ADE-b	44	44	45	28	28	28	27	27	27
Girls	ADE-b	62	62	62	27	27	27	11	11	11
Boys	ADE	—	—	32	—	—	30	—	—	38
Girls	ADE	—	—	51	—	—	28	—	—	21
Boys	AE-b	72	73	74	28	27	26	—	—	
Girls	AE-b	74	75	76	26	25	24	—	—	
Age 12 year										
Boys	ADE	—	—	36	—	—	31	—	—	33
Girls	ADE	—	—	68	—	—	28	—	—	5
Boys	AE	—	—	68	—	—	32	—	—	—
Girls	AE	—	—	72	—	—	28	—	—	—

A, additive genetic; D, dominance genetic; E, unique environment; −b, contrast parameter.
[a]Corrected for any variance induced by the contrast effect; these estimates are usually reported by other behavior genetic studies of ADHD phenotypes for which a contrast effect is detected.

by discussion of clinical implications and limitations of this study.

Phenotypic Findings

With respect to the differences between genders, boys are reported as displaying more overactivity and attention problems as compared to girls. For the subsample that is likely to meet a DSM diagnosis of ADHD, we observed a boy-to-girl ratio of 1.5 to 1 at ages 3, 10, and 12 years. A gender ratio of 2 to 1 was observed at the age of 7 years. In line with our outcome, the meta-analysis by Gaub and Carlson [1997] indicated that non-referred samples of girls with ADHD relative to the boys with ADHD show indeed lower levels of attention problems. Although not all studies agree on the presence of varying degree of behavioral problems between pre-school boys and girls [Campbell, 1995], we report upon a significant gender effect for overactive behavior in 3-year-old children. An increase in symptom counts from preschool age to school age was observed for boys. Entering puberty, both boys and girls displayed a decrease in problem behavior. The age-dependent decline of inattention symptoms confirms the outcomes reported by Biederman et al. [2000]. Unfortunately, even though the inattention symptoms decline, it is known from multiple studies that many of these children continue to have emotional and behavioral problems, sometimes severe [Rutter et al., 1998].

Genetic and Environmental Estimates Across the age

For the overactivity syndrome at the age 3 years and the attention problems syndrome at ages 7, 10, and 12 years, we analyzed several models, and in each case several models fitted the data. Each acceptable model included genetic, either additive or additive and dominance effects, and unique environmental effects. The broad heritability estimates, when dominance and additive relative estimates are summed, were high, ranging from 68% to 76% across age. In the previous research on attention problems and associated phenotypes, additive genetic influences ranging from 60% to 80% were found, depending on the model and the gender of the subjects [Nadder et al., 1998; Simonoff et al., 1998; Rhee et al., 1999; Eaves et al., 2000; Hudziak et al., 2000; Thapar et al., 2000; Martin et al., 2002]. Environmental influences that are unique to the individual contribute to one third of the total variance observed for overactivity and attention problem behavior. Shared environmental factors, those that influence siblings more similar are negligible. The consistency in results across these large twin studies is notable, considering the variety in assessment instruments, method of data collection, methods of analyses, and age of the twins.

As opposed to the large number of behavior genetic studies on problem behavior in school aged children, only few studies have reported upon activity in preschool children [Price et al., submitted; Saudino et al., 2000]. Given the large samples, there is now convincing evidence to conclude that hyperactive/overactive behavior in pre-school children is largely genetic with estimated heritability of around 70%. In addition to the additive genetic effects, contrast effects explain a significant proportion of the variance in hyperactive/overactive behavior at this young age. With respect to the genetic dominance, this source of variance in preschool children can not be excluded. Numerous other studies have reported upon dominance effects for prepubertal children or young adolescents. However, they have done so by means of analyses of even smaller datasets that are often pooled across age [see for review

Thapar et al., 1995; Kuntsi and Stevenson, 2000; Kuntsi et al., 2000]. If data of different ages are merged, a possible diminishing impact of genetic dominance and/or contrast effect at older ages may be masked by the prominent presence of this source of variance at younger ages. Thus it remains unclear from prior studies if dominance and/or contrast effects are prominent when children enter puberty. Despite this shortcoming, given the large agreement across studies, there is little doubt on the importance of (broad) heritability in explaining variance for attention problems and related symptoms, from infancy to young adulthood.

Gender Differences

Another important finding is the presence of gender differences in the variance estimates at ages 10 and 12 years. Here, the evidence supports larger variances for boys at the ages 10 and 12 years. A possible explanation for this difference in variance is that the genetic effect, which is shared by both genders, has been amplified in boys as compared to girls. When variance components are expressed as a proportion of the total variance, we obtained equal estimates for broad heritability and the unique environment. This implies that the pattern of additive genetic, dominance genetic, and unique environmental effects is similar in boys and girls. With the exception of Rhee et al. [1999], this outcome agrees with reports by other large twin studies [Nadder et al., 1998; Thapar et al., 2000].

Contrast Effect

An interesting observation appeared when means across zygosities were evaluated. Girls with a male co-twin were rated to display less overactivity and attention problems compared to girls with a female co-twin. This effect was not reversed; boys with a female co-twin were rated as having an equal degree of problem behavior as other twin boys. This finding suggests that the male twin serve as some kind of protective factor for his female sibling. The mechanism underlying this protective factor is speculative. Given the less likely situation that the opposite-sex female twins truly display less overactivity and attention problems as compared to any other group of twins, the mechanism appears to be related to the person who rates the behavior. Since overactivity and attention problems are more recognized and often occur with other externalizing behaviors in boys [Gaub and Carlson, 1997], mothers may tend to evaluate the behavior of their daughter in comparison to their son as 'not as much.' This speculation implies a bias in the mean values introduced by the mother. In our genetic modeling, evaluation of bias took place by the analysis of variance. We considered three types of contrast parameters, one for male same-sex twins, one for female same-sex twins, and one for the opposite-sex twins. In our preliminary analyses, we established that the magnitude of the contrast effect in opposite-sex twins did not differ from the mean value of the contrast effect in male pairs and female pairs. This finding does not exclude the possibility that, only in opposite-sex pairs, gender does play a role in explaining a part of the variance. So, instead of the specification of one contrast effect, it may be interesting to disentangle the contrast further into an effect from-boy-to-girl and an effect from-girl-to-boy [Eaves et al., 2000]. Post hoc, we performed such an exploration of the contrast effect in 3-year-old opposite-sex twins. In line with our expectation, the effect from-boy-to-girl was found to be much larger compared to the effect from-girl-to-boy (-0.17 vs. -0.05).

The largest contrast effect was detected at the age of 3 years. With respect to our sample size and the magnitude of the effect ($-0.12/-0.14$), we have sufficient power to confirm the presence of the contrast effect. Several studies on ADHD and related phenotypes have reported upon the absence of a contrast effect in teacher- or observer-data [Sherman et al., 1997; Simonoff et al., 1998; Kuntsi et al., 2000; Saudino et al., 2000; Nadder et al., 2001; Martin et al., 2002]. These outcomes confirm our conclusion based on the pattern in means and point to a rater bias effect. The implication of a rater bias in diagnosis and research is clear. Bias can lead to misdiagnoses in the clinical setting and the inclusion of false positives or exclusion of true cases from gene searching efforts, both of which are undesirable. If a gene finding study is designed to select discordant twin pairs and concordant twin pairs, the former group would be over-represented and the latter group would be under-represented due to maternal rater bias.

The Dutch overactivity scale and the attention problem scale of the CBCL appear a suitable instrument for case identification, as part of the sample selection for gene searching research. We do not suggest that these scales should be used as the sole measuring stick for molecular genetic studies of ADHD, but rather as a phenotypic marker to improve our ability to minimize false positives and negatives.

Clinical Implications, Limitations, and Future Research

These data may help us understand similarities and differences between studies of DSM-IV ADHD, that identify four times more boys than girls as having ADHD, versus studies of attention problems, for which the gender ratio is much less marked. The DSM lacks normative data by gender whereas the CBCL compares deviance in boys and girls only against data on other boys and girls, respectively, of the same age. To date there have been no compelling arguments to explain the gender differences in the prevalence of ADHD. Perhaps part of the explanation has to do with the taxonomy and gender-genetic factors. Because the CBCL is normed by age, gender, and is less likely to be affected by rater contrast, the data support the consideration of using the attention problems scale in the clinical setting. The application of the attention problems scale may improve the ability to screen for ADHD in siblings of ADHD children when maternal endorsement of DSM items do not support the diagnoses of ADHD in a 'less affected sibling.' Similarly, because the CBCL is normed by gender, use of this scale may allow the clinician to identify girls who are at risk for ADHD, who might not

appear as deviant as their brothers based on the fact that all girls have fewer symptoms than boys. Finally, consideration of these data in the clinical setting may increase the awareness of the quantitative nature of overactivity and attention problems in children with emotional and behavioral problems. Instead of requiring a child to meet an absolute number of symptoms, the clinician can use this quantitative scale to assess severity, social, personal, and emotional impairment, and treatment response.

With respect to limitations of the study we note the following. Our genetic modeling results indicate that genetic influences are important and fairly stable in magnitude over the course of a 9-year developmental period. The development of attention problems has been well documented [Barkley et al., 1990; Weiss and Hechtman, 1993]. Here we do not comment on longitudinal aspects of the data but focus on heritability at each age. Currently, data from additional birth-cohorts are added to the dataset. The enlarged sample of the same twins assessed at multiple occasions in time makes longitudinal analyses possible. This work is now underway and results will appear in a separate report.

A second limitation from a clinical point of view is that we use the CBCL to assess for AP and not DSM-IV criteria. Thus, although AP is highly predictive of ADHD, it is not ADHD. Although data have been presented on the relations between AP and ADHD, conclusions about AP may not generalize to genetic studies of ADHD. The oucomes obtained by a large twin study confirm the variety in outcomes when different assessment instruments are used [Thapar et al., 2000].

We mentioned that we obtained likewise results by analyses of paternal data, compared to the maternal data which we have reported here. Although it was established that a rater bias effect is of minimal influence beyond age the of 3 years, this does not exclude the possibility that mothers and fathers underscore the presence of inattention in their children [Klein and Mannuzza, 1991]. Recently, the study is extended with the collection of teacher report data, youth self report data, and DSM-IV interview data. This wealth of data enables us to investigate the genetic and environmental influences on the development of attention problems from multiple points of view.

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REFERENCES

Achenbach TM. 1991. Manual for the child behavior checklist/4-18. Burlington, VT: University of Vermont Department of Psychiatry.

Barkley RA, Fisher M, Edelbrock CS, Smallish L. 1990. The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. J Am Acad Child Adolesc Psychiatr 29:546–557.

Barr C, Swanson J, Kennedy J. 2001. Molecular genetics of ADHD. In: Levy F, Hay DA, editors. Attention, genes and ADHD. East Sussex: Brunner-Routledge. p 173–195.

Biederman J. 1998. Attention-deficit/hyperactivity disorder: A life-span perspective. J Clin Psychiatry 59:4–16.

Biederman J, Faraone SV, Doyle A, Lehman BK, Kraus I, Perrin J, Tsuang MT. 1993. Convergence of the child behavior checklist with structured interview-based psychiatric diagnoses of ADHD children with and without comorbidity. J Child Psychol Psychiatr 34:1241–1251.

Biederman J, Mick E, Faraone SV. 2000. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: Impact of remission definition and symptom type. Am J Psychiatry 157:816–818.

Bird HR, Canino G, Rubio-Stipec M, Gould MS, Ribera J, Sesman M, Woodbury M, Huertas-Goldman S, Pagan A, Sanchez-Lacay A, Moscoso M. 1988. Estimates of the prevalence of childhood maladjustment in a community survey in Puerto Rico. The use of combined measures [published erratum appears in *Arch Gen Psychiatr 1994, 51:429*]. Arch Gen Psychiatr 45:1120–1126.

Boomsma DI. 1998. Twin registers in Europe: An overview. Twin Res 1:34–51.

Campbell SB. 1995. Behavior problems in preschool children: A review of recent research. J Child Psychol Psychiatr 36:113–149.

Carey G. 1986. Sibling imitation and contrast effects. Behav Genet 16:319–341.

Chen WJ, Faraone SV, Biederman J, Tsuang MT. 1994. Diagnostic accuracy of the child behavior checklist scales for attention-deficit hyperactivity disorder: A receiver-operating characteristic analysis. J Consult Clin Psychol 62:1017–1025.

Eaves LJ. 1976. A model for sibling effects in man. Heredity 36:205–214.

Eaves LJ, Silberg JL, Maes HH, Simonoff E, Pickles A, Rutter M, Neale MC, Reynolds CA, Erikson MT, Heath AC, Loeber R, Truett KR, Hewitt JK. 1997. Genetics and developmental psychopathology: 2. The main effects of genes and environment on behavioral problems in the Virginia twin study of adolescent behavioral development. J Child Psychol Psychiatr 38:965–980.

Eaves LJ, Rutter M, Silberg JL, Shillady L, Maes HH, Pickles A. 2000. Genetic and environmental causes of covariation in interview assessments of disruptive behavior in child and adolescent twins. Behav Genet 30:321–334.

Edelbrock C, Costello AJ. 1988. Convergence between statistically derived behavior problem syndromes and child psychiatric diagnoses. J Abnorm Child Psychol 16:219–231.

Edelbrock C, Rende R, Plomin R, Thompson LA. 1995. A twin study of competence and problem behavior in childhood and early adolescence. J Child Psychol Psychiatr 36:775–785.

Falconer DS, Mackay TFC. 1996. Introduction to quantitative genetics (4th ed.). Essex: Addison Wesley Longman Limited. 299 p.

Faraone SV, Doyle AE. 2001. The nature and heritability of attention-deficit/hyperactivity disorder. Child Adolesc Psychiatr Clin N Am 10:299–316.

Gaub M, Carlson CL. 1997. Gender differences in ADHD: A meta-analysis and critical review. J Am Acad Child Adolesc Psychiatr 36:1036–1045.

Hartung CM, Widiger TA. 1998. Gender differences in the diagnosis of mental disorders: Conclusions and controversies of the DSM-IV. Psychol Bull 123:260–278.

Hudziak JJ. 2001. The role of phenotypes (diagnoses) in genetic studies of attention-deficit/hyperactivity disorder and related child psychopathology. Child Adolesc Psychiatr Clin N Am 10:279–297.

Hudziak JJ. 2002. The importance of phenotype definition in genetic studies of child psychopathology. In: Helzer JE, Hudziak JJ, editors. Defining psychopathology in the 21st century: DSM-V and beyond. American Psychiatric Publishing Group, Inc. 211–230.

Hudziak JJ, Rudiger LP, Neale MC, Heath AC, Todd RD. 2000. A twin study of inattentive, aggressive and anxious/depressed behaviors. J Am Acad Child Adolesc Psychiatr 39:469–476.

Hudziak JJ, Heath AC, Madden PAF, Reich W, Bucholz KK, Slutske WS, Bierut LJ, Neuman RJ, Todd RD. 2002. In review. The genetic analysis of parental reports of DSM-IV. J Am Acad Child Adolesc Psychiatr.

Jöreskog KD, Sörbom D. 1993. New features in PRELIS 2. Chicago: Scientific Software International, Inc.

Klein RG, Mannuzza S. 1991. Long-term outcome of hyperactive children: A review. J Am Acad Child Adolesc Psychiatr 30:383–387.

Koot HM, van den Oord EJCG, Verhulst FC, Boomsma DI. 1997. Behavioural and emotional problems in young pre-schoolers: Cross-cultural testing of the validity of the child behavior checklist 2/3. J Abnorm Child Psychol 25:183–196.

Kuntsi J, Stevenson J. 2000. Hyperactivity in children: A focus on genetic research and psychological theories. Clin Child Fam Psychol Rev 3: 1–23.

Kuntsi J, Gayán J, Stevenson J. 2000. Parents' and teachers' ratings of problem behaviours in children: Genetic and contrast effects. Twin Res 3:251–258.

Loehlin JC. 1992. Latent variable models: An introduction to factor, path, and structural analysis. Hillsdale, New Yersey: Lawrence Erlbaum Associates.

Martin N, Scourfield J, McGuffin P. 2002. Observer effects and heritability of childhood attention-deficit hyperactivity disorder symptoms. Br J Psychiatr 180:260–265.

Nadder TS, Silberg JL, Eaves LJ, Maes HH, Meyer JM. 1998. Genetic effects on ADHD symptomatology in 7- to 13-year-old twins: Results from a telephone survey. Behav Genet 28:83–100.

Nadder TS, Silberg JL, Rutter M, Maes HH, Eaves LJ. 2001. Comparison of multiple measures of ADHD symptomatology: A multivariate genetic analysis. J Child Psychol Psychiatr 42:475–486.

Neale MC. 1997. Mx: Statistical modeling. Richmond, VA: Department of Psychiatry, Medical College of Virginia.

Neale MC, Cardon LR, North Atlantic Treaty Organization. Scientific Affairs Division. 1992. Methodology for genetic studies of twins and families. Dordrecht: Kluwer Academic Publishers.

Neale MC, Stevenson J. 1989. Rater bias in the EASI temperament scales: A twin study. J Pers Soc Psychol 56:446–455.

Offord DR, Boyle MH, Szatmari P, Rae-Grant NI, Links PS, Cadman DT, Byles JA, Crawford JW, Blum HM, Byrne C, et al. 1987. Ontario child health study. II. Six-month prevalence of disorder and rates of service utilization. Arch Gen Psychiatr 44:832–836.

Plomin R, DeFries JC, McClearn GE, McGuffin P. 2001. Behavior genetics (4th ed.). New York: W.H. Freeman.

Rhee SH, Waldman ID, Hay DA, Levy F. 1999. Sex differences in genetic and environmental influences on DSM-III-R attention-deficit/hyperactivity disorder. J Abn Psychol 108:24–41.

Rietveld MJH, Posthuma D, Dolan CV, Boomsma DI. ADHD: sibling interaction or dominance. An evaluation of statistical power. Beh Genet (in press).

Rietveld MJH, van der Valk JC, Bongers IL, Stroet TM, Slagboom PE, Boomsma DI. 2000. Zygosity diagnosis in young twins by parental report. Twin Res 3:134–141.

Ross DM, Ross SA. 1982. Hyperactivity. Current issues, research, and theory. New York: John Wiley & Sons, Inc.

Rutter M, Giller H, Hagell A. 1998. Antisocial behavior by young people. New York/Cambridge: Cambridge University Press.

Saudino KJ, Cherny SS, Plomin R. 2000. Parent ratings of temperament in twins: Explaining the 'too low' DZ correlations. Twin Res 3:224–233.

Schmitz S, Fulker DW, Mrazek DA. 1995. Problem behavior in early and middle childhood: An initial behavior genetic analysis. J Child Psychol Psychiatr 36:1443–1458.

Sherman DK, Iacono WG, McGue MK. 1997. Attention-deficit hyperactivity disorder dimensions: A twin study of inattention and impulsivity-hyperactivity. J Am Acad Child Adolesc Psychiatr 36:745–753.

Simonoff E, Pickles A, Hervas A, Silberg JL, Rutter M, Eaves L. 1998. Genetic influences on childhood hyperactivity: contrast effects imply parental rating bias, not sibling interaction. Psychol Med 28:825–837.

Steingard R, Biederman J, Doyle A, Sprich-Buckminster S. 1992. Psychiatric comorbidity in attention deficit disorder: Impact on the interpretation of child behavior checklist results. J Am Acad Child Adolesc Psychiatr 31:449–454.

Thapar A, Hervas A, McGuffin P. 1995. Childhood hyperactivity scores are highly heritable and show sibling competition effects: Twin study evidence. Behav Genet 25:537–544.

Thapar A, Harrington R, Ross K, McGuffin P. 2000. Does the defninition of ADHD affect heritability? J Am Acad Child Adolesc Psychiatr 39:1528–1536.

Weiss G, Hechtman L. 1993. Hyperactive children grown up. ADHD in children, adolescents and adutls. (2nd ed.). New York: Guilford Press.